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A chiral molecular recognition approach to the formation of optically active quaternary centres in aza-Henry reactions

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An approach to asymmetric catalysis based on chiral molecular recognition by the combination of chiral Lewis acids and chiral organocatalysis for the formation of optically active quaternary centers in the aza-Henry reaction is presented; this procedure leads to products with up to 98% ee and a diastereomeric ratio of 14 : 1 in excellent yields with catalyst loadings of 5 mol%.

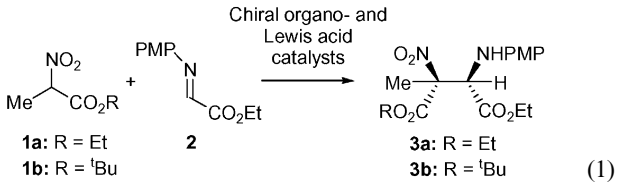
The formation of chiral quarternery centres is a challenge to modern organic chemistry since a lot of natural compounds contain this motif.[1] Catalysis based on chiral Lewis acids is a well-established methodology, however, some limitations in terms of lack of control of tertiary substrates have been observed. Asymmetric organocatalysis using chiral cinchona alkaloids has seen a rise of interest in recent years.[2] Such compounds can be very selective, but can also suffer from lack generality.

In classic chiral Lewis-acid catalysis, the chiral ligand will screen one of the *Re*- or *Si*-faces of the electrophile from attack. In a situation where the nucleophile is a chiral tertiary anion the catalyst must, in order to obtain diastereoselectivity, also distinguish between the two easily interchangeable enantiomers of the anion. Here, a single activation strategy might fail, affording the product in high enantioselectivity, but with low (or no) diastereoselectivity.

We envisioned a strategy for controlling the assembly of tertiary nucleophiles with electrophiles in which a chiral Lewis acid catalyst activates the electrophile and organocatalytic activation of the nucleophile thereby generates a diastereomeric pair (Scheme 1).[3] This renders diastereoselectivity a matter of molecular recognition between diasteromeric compounds. In this way, we hoped to find a matched set of catalysts to assemble complex structures in asymmetric catalysis.

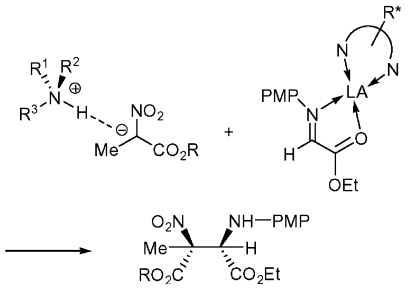
As a model system we chose the aza-Henry (or nitro-Mannich) reaction,[4] employing a tertiary nitro compound as a nucleophile (Scheme 1). Since our initial reports on enantio- and diastereoselective aza-Henry reactions[5] a number of reports have appeared.[6]

Initially, 2-nitro propanoic acid ethyl ester **1a** was reacted with (*p*-methoxyphenylimino)acetic acid ethyl ester **2** (eqn. 1) in the presence of 20 mol% (*R*)-Ph-BOX[7] and $Cu(OTf)_2$ using Et_3N as the base in CH_2Cl_2. This afforded the aza-Henry adduct **3a** in 95% conversion, 66% ee and a diastereomeric ratio of 1 : 1, while no reaction takes place in the absence of the organic base (Table 1, entries 1–2). Changing to the more bulky Hünigs base afforded the aza-Henry adduct **3a** in 70% ee, but still in a 1 : 1 ratio of diastereomers (entry 3). It was envisioned that changing to the more bulky 2-nitro propanoic acid *tert*-butyl ester **1b** would afford a higher selectivity, however only a slight improvement of the diastereoselectivity (to 2 : 1) was obtained; but (to our satisfaction) the enantioselectivity of the two disatereomers increased to 80 and 82% ee, respectively (entry 5).



(1)

Thus we began the screening of a series of chiral bases in combination with Cu(II) catalysts. Quinine and Cu(II), in the absence of the chiral BOX-ligand, lead to a low conversion giving **3b** in a 1 : 1 ratio (entry 6).† Adding the non-chiral ligands phenanthroline or 2,2-bipyridine to $Cu(OTf)_2$ raises the conversion to 27 and 50%, and affords a diastereomeric ratio of 8 : 1 and 7 : 1, respectively. However, the product was racemic. The latter results show that a ligand accelerating effect is observed. Using quinine, without a Lewis acid, affords no conversion.



Scheme 1

Table 1 Some screening results for stereoselective aza-Henry reaction using achiral and chiral $Cu(OTf)_2$ complexes and organocatalysts

Entry	1	Ligand	Base	Conversion (%)	Dr	Ee (%)[a]
1	**a**	(*R*)-Ph-BOX	—	<5	—	—
2	**a**	(*R*)-Ph-BOX	Et_3N	95	1 : 1	—/66
3	**a**	(*R*)-Ph-BOX	Hünig	82	1 : 1	49/70
4	**a**	(*R*)-Ph-BOX[b]	—	54	1 : 1	0/24
5	**b**	(*R*)-Ph-BOX	Et_3N	>90	2 : 1	80/82
6	**b**	—[c]	Quinine	14	1 : 1	0/0
7	**b**	Phenanthroline	Quinine	27	8 : 1	0/0
8	**b**	2,2-Bipyridine	Quinine	50	7 : 1	0/0
9	**b**	—[d]	Quinine	0	—	—

[a] The numbers refer to the ee of both stereomers. [b] $Cu(OAc)_2$ was used as Lewis acid. [c] Only $Cu(OAc)_2$ present. [d] No Lewis acid present.

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Table 2 Different combinations of cinchona alkaloids and (*R*)-Ph-BOX-Cu(OTf)$_2$ for the aza-Henry reaction

Entry	Base	Loading (mol%)	Yield (%)	Dr	Ee (%)[a]
1	Quinine	20	90	14 : 1	98
2	Quinidine	20	80	8.5 : 1	96
3	Cinchonine	20	76	7 : 1	94
4	Quinine[b]	20	76	8.5 : 1	−93
5	Hydroquinine	20	90	10 : 1	95
6	Quinidine[b]	20	90	8 : 1	−91
7	Hydrocinchonine	20	90	7 : 1	93
8	(DHQ)$_2$PHAL	20	83	2 : 1	85
9	(DHQD)$_2$PHAL	20	82	3 : 1	30
10	Quinine	10	90	14 : 1	98
11	Quinine	5	85	14 : 1	98
12	Quinine	1	20	—	75

[a] Ee of major diastereomer. [b] (*S*)-Ph-BOX was used as the chiral Lewis acid.

These findings imply that the enantioselectivity is controlled by the chiral Lewis acid and the diastereoselectivity by the cinchona alkaloid.

We were delighted to find that using quinine as the chiral base in combination with (*R*)-Ph-BOX-Cu(OTf)$_2$ (Fig. 1) afforded, for the reaction of 2-nitro propanoic acid *tert*-butyl ester **1b** with (*p*-methoxyphenylimino)acetic acid ethyl ester **2**, the aza-Henry adduct **3b** in 98% ee and a diastereomeric ratio of 14 : 1 with full conversion (Table 2, entry 1). For the similar reaction of 2-nitro propanoic acid ethyl ester **1a**, the diastereomeric ratio remained 2 : 1 using quinine as the base, which indicates that the *tert*-butyl ester is essential for the specific interaction with the cinchona base.

A series of cinchona alkaloids was investigated in order to obtain information about the catalytic system (Table 2). Quinidine, being the pseudo enantiomer of quinine, in combination with (*R*)-Ph-BOX-Cu(OTf)$_2$, reduce the diastereomeric ratio to 8.5 : 1, however, the high enantioselectivity (96% ee) was maintained (entry 2). This implies that this combination is to some extent a mismatched pair of catalysts. Performing the reaction with cinchonidine afforded little change in stereoselection, although this cinchona alkaloid has been stated to be less basic than quinine (entry 3). Lowering the catalyst loading to 5 mol% gave no reduction of activity since both enantio- and diastereoselectivity were maintained. Performing the reaction with 1 mol% of the catalyst resulted in a drop in enantioselectivity to 75% and a conversion of 20%.

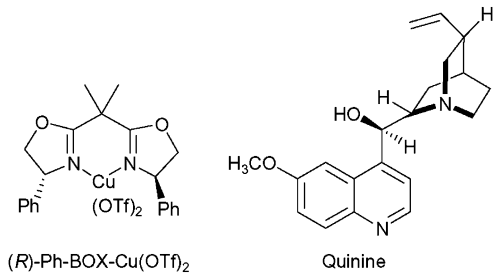
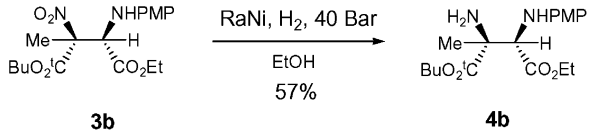


Fig. 1 The best chiral copper(II) bisoxazoline complex and chinchona alkaloid found for the screening of the aza-Henry reaction.

The use of hydroquinine as the chiral base, *i.e.* quinine with a hydrogenated double bond, afforded comparable results to the use of quinine (entry 5). The dimeric cinchona alkaloids such as (DHQ)$_2$PHAL or (DHQD)$_2$PHAL gave moderate enantioselectivity and low diastereoselection (entries 8–9). These findings support that a molecular recognition between the chiral Lewis acid ligand and the cinchona alkaloid is responsible for the observed selectivity.

Interestingly an inversion of stereochemistry is observed when the reaction is performed with the (*S*)-enantiomer of the Ph-BOX ligand and quinine, and a reduction in diastereomeric ratio is observed (entry 4). The reaction with quinidine and (*S*)-Ph-BOX as the chiral Lewis acid ligand gives also the opposite enantiomer in a diastereomeric ratio of 8.5 : 1 (entry 6). Hence the enantioselectivity is governed solely by the chiral Lewis acid ligand.

The formed nitroamine **3b** can easily be transformed into the corresponding diamine **4b** using Ra–Ni as a hydrogenation catalyst in 57% yield (Scheme 2).‡ The moderate yield is probably due to product coordination to nickel. The use of EtOH as solvent is crucial, since reaction performed in MeOH affords decomposition products.



3b **4b**

Scheme 2

In conclusion, we have developed a novel methodology in asymmetric synthesis using a dual chiral activation based on molecular recognition by a cinchona alkaloid and a chiral Lewis acid complex. We have shown the efficiency in forming products in high enantioselectivity and diastereomeric ratio using low catalytic loadings. The facile reduction to a chiral diamine has been shown.

Notes and references

† **3-(4-Methoxyphenylamino)-2-methyl-2-nitrosuccinic acid 1-*tert*-butyl ester 4-ethyl ester 3b.** To a flame dried Schlenk flask was added Cu(OTf)$_2$ (18.4 mg, 0.05 mmol). The flask was evacuated and dried with a heat gun for 1 min. (*R*)-Ph-box (18.2 mg. 0.055 mmol) was added and stirred under vacuum for 30 min. CH_2Cl_2 (2 mL) was added under N_2 and the mixture was stirred for 1 h. (4-Methoxyphenylimino)acetic acid ethyl ester (51.8 mg, 0.25 mmol) was added followed by quinine (16.2 mg, 0.050 mmol) and 2-nitro propanoic acid *tert*-butyl ester (65.7 mg, 0.38 mmol). The reaction was stirred for 48 h and filtered through a plug of silica to remove the catalyst. Purified on flashmaster using an ether/pentane gradient. Isolated yield 90%. $[\alpha]_D^{20} = +7.5$ ($c = 0.01$ $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.76 (m, 4H), 4,60 (d, $J = 11.4$ Hz, 1H), 4.48 (d, $J = 11.4$ Hz, 1H), 4,14 (q, $J = 7.0$ Hz, 2H), 3.73 (s, 3H), 2.04 (s, 3H), 1.41 (s, 9H), 1.18 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.68, 164.73, 153.97, 140.67, 116.97, 116.80, 114.98, 114.86, 96.00, 85.38, 63.86, 62.36, 55.78, 27.80, 21.20, 14.15; mass (TOF ES$^+$): m/z 405; HRMS calculated for $C_{18}H_{26}N_2O_7Na$ 405.1638 found 405.1646.

‡ **3-(4-Methoxyphenylamino)-2-methyl-2-aminosuccinic acid 1-*tert*-butyl ester 4-ethyl ester 4b.** (160 mg, 0.42 mmol) of **3b** was dissolved in EtOH (10 mL) in a high pressure bomb and Ra–Ni 20 mg was added. The atmosphere was substituted with N_2 followed by H_2 at 40 bar. The reaction was stirred for 24 h and the catalyst was filtered of followed by removal of the solvent *in vacuo* affording the title product as a clear oil. Isolated yield 84 mg, 57%. $[\alpha]_D^{20} = -4.9$ ($c = 0.3$ $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.68 (d, $J = 8.8$ Hz, 2 H), 6.59 (d, $J = 8.8$ Hz. 2H), 4.44 (d, $J = 10.8$ Hz, 1H), 4.21 (d, $J = 10.8$ Hz, 1 H), 4.10 (q, $J = 7.0$ Hz, 2H), 3.66 (s, 3H) 1.71(bs, 2H) 1.35 (m, 12H) 1.16 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR

($CDCl_3$) δ 173.96, 172.29, 153.06, 141.27, 116.05, 115.46, 114.99, 114.85, 82.21, 64.30, 61.31, 60.51, 55.87, 28.07, 25.77, 14.52; mass (TOF ES^+): m/z 353; HRMS calculated for $C_{18}H_{29}N_2O_5^+$ 353.2076 found 353.2086.

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